IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	KIM, et al.	
SERIAL NO.	:	10/016,812	
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FOR	:	RAPIDLY DISINTEGRABLE TABLET FOR ORAL ADMINISTRATION	
EXAMINER	:	CHOI, Frank I.	ART UNIT: 1616

To: Honorable Commissioner of Patents
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. SECTION 1.132

Sir:

I, Hyun-soo KIM, being a citizen of the Republic of Korea and presently residing at Baekdoo Apt. 968-403, Sanbon-dong, Kunpo-si, Kyonggi-do, Korea, hereby declare as follows:

1. I am one of the inventors of the above-identified application.

2. I have performed a series of experiments to compare the inventive tablets with the tablets according to the prior arts, as follows.

3. Specifically, 10 g of donepezil hydrochloride and 2 g of silicon dioxide, each screened through a 30 mesh sieve, were mixed and added thereto was 200 g of spray-dried mannitol (180 ㎛, Pearlitol SD 200, Roquette). The mixture was further mixed with 15 g of crospovidone powder (110 ㎛), and then with 3 g of aspartame and 5 g of magnesium stearate, each screened through a 40 mesh sieve (see Table 1). The resultant mixture was compressed into tablets using a single type tableting machine (Manesty F3, Manesty Machine Ltd.), to provide rapidly disintegrable tablets (Tablet A), each weighing 250 mg.

   The above procedure was repeated using the components shown in Table 1 to obtain Tablets B to F. At this time, the cellulose components were screened

through a 20 mesh sieve.

The hardness, the disintegration time in oral cavity and organoleptic feeling property were measured for Tablets A to F in accordance with the method disclosed in the specification of the present invention as originally filed (see page 13, line 11 to page 14, line 3).

<Table 1>

(Unit : gram)

		Tablet A (Present Invention)	Tablet B	Tablet C	Tablet D	Tablet E	Tablet F (The '292 Patent)
Drug	Donepezil hydrochloride	10	10	10	10	10	10
Disintegrant	Spray-dried mannitol (180㎛)	200	180	180	180	-	-
	D-mannitol (45㎛)	-	-	-	-	200	180
	Crospovidone (110㎛)	15	15	15	15	15	15
Diluent	Crosslinked carboxymethyl cellulose	-	20	-	-	-	20
	Hydroxypropyl cellulose	-	-	20	-	-	-
	Hydroxypropyl methylcellulose				20		
Sweetening agent	Aspartame	3	3	3	3	3	3
Lubricant	Silicon dioxide	2	2	2	2	2	2
	Magnesium Stearate	5	5	5	5	5	5
Total weight (mg)		250	250	250	250	250	250
Tablet Diameter (mm)		11.0	11.0	11.0	11.0	11.0	11.0
Number of tablets		1,000	1,000	1,000	1,000	1,000	1,000
Hardness(kp)		5	5	5	5	5	5
Disintegration time in the oral cavity (second)		40	95	110	115	120	140
Organoleptic feeling (+++ : Very good, ++: Good)		+++	++	+	+	+	+

4. Table 1 shows that the inventive rapid disintegrable tablet (Tablet A) using a spray-dried mannitol instead of a combination of D-mannitol with a cellulose

compound as disclosed in the primary reference cited by the Examiner (WO 00/78292) (Tablet F) provides a remarkably reduced disintegration time in the oral cavity. Further, as can be seen from the comparison of Tablet E with Tablet F, if the cellulose compound were excluded from the tablet of the '292 patent to employ D-mannitol alone, the disintegration time of the tablet thus produced can be somewhat reduced, although insufficient. That is, the use of a cellulose compound in a rapid disintegrable tablet in the oral cavity makes the tablet to be less disintegrable and less water-soluble.

Similarly, from the comparison of Tablet F with Tablets B to D, even if a spray-dried mannitol according to the '777 patent is introduced into the tablet according to the '292 patent in place of D-mannitol, the disintegration time of the resulting tablets are still long due to the use of the cellulose compound.

As mentioned above, in accordance with the present invention, rapid-disintegrable tablets which disintegrate within 60 seconds in the cavity can be obtained by way of using spray-dried mannitol instead of D-mannitol, without a cellulose compound; and, such inventive constitution and effect are unique feature which cannot be conceived from simple combination of the '292 patent and the '777 patent.

5. I hereby declare that all statements made herein of our own knowledge are true and all statements made on information and belief are believed to be true; and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of United States Code and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

Further deponents saith not.

Date: 6 th day of April, 2007

Hyun Soo Kim

(Hyun-soo KIM)

A New Method for Disintegration Studies of Rapid Disintegrating Tablet

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The aim of this study was to develop a simple and suitable disintegration method specific for rapid disintegrating tablets (RDTs). The new disintegration method that we propose employs a rotary shaft to exert mechanical pressure on the RDT. To assess our method, we manufactured several placebo RDTs and exposed them to severe storage conditions (60°C/75%RH for 1week) in order to obtain RDTs with a wide range of disintegration times. These placebo RDTs were utilized to compare the disintegration times obtained by several methods, including the proposed method. As expected, the disintegration time of the placebo RDTs in human sensory test varied widely. The disintegration times determined by the conventional disintegration test were in good correlation to those in human sensory test, but the slope was far from 1 (0.241). There was no correlation between the disintegration time of RDTs in human sensory test and those determined by the conventional dissolution test. In contrast, we acquired good correlation between the disintegration times obtained with the new method and those in human sensory test, and the slope was very close to 1 (0.858). We attribute this to the use of mechanical stress in the new method, similar to that the RDT is subject to in the oral cavity. We therefore concluded that the proposed method was suitable for the measurement of the disintegration time of RDTs. This new method might provide a valuable approach for the establishment of the official disintegration test for RDTs in the future.

Key words rapid disintegrating tablet (RDT); disintegration method; mechanical stress

In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life (QOL), most of these efforts have been focused on ease of medication[1—3] or novel drug delivery systems.[4—6] Among the dosage forms developed to facilitate ease of medication, the rapid-disintegrating tablet (RDT) is one of the most widely employed as commercial products.[7—9] The RDT has remarkable disintegration properties; without water, it is rapidly disintegrated in the mouth within only a few seconds. When the RDT is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration.

Until recently, the friability of the RDT was considered a critical problem. However, the utilization of the molding tabletting machine developed by Eisai Co. Ltd. has solved these counterpoints (disintegration and friability).

The RDT presents considerable advantages for the patient (or elder) who has a swallow dysfunction, or who is not permitted water intake because of disease.[10] One of the most important characteristics of the RDT is its disintegration time in the oral cavity; however, a suitable method to access the disintegration properties described in the Pharmacopoeias (Japan, U.S.A. or Europe) has not been developed.

At present, the disintegration time of RDTs is measured utilizing the conventional tests (for tablets) that are described in the Pharmacopoeias. However, it is difficult to assess the disintegration rate for the RDT with these tests due to its rapid disintegration rate even in a small amount of water. Further, the conventional tests employ a volume of 900 ml of test solution compared to the volume of saliva in humans, which is less than 1 ml. Thus, the disintegration rate obtained from the conventional disintegration tests appears not to be reflective of the disintegration rate in the human mouth.[11—13]

To overcome this problem, several new methods have been proposed. These methods employ a modified dissolution test,[11] fluid water[12] or a CCD camera.[13] However, we consider that these methods might not be efficient because the RDT does not receive any mechanical stress force. In fact, the RDT receives some mechanical stress produced by the tongue in the human mouth. The purpose of this study was to establish a suitable disintegration method for RDT. In the experimental method that we propose herewith, the RDT is placed on a stainless steel wire gauze, which is slightly immersed in medium (Fig. 1), and a rotary shaft is employed to provide mechanical stress to the tablet by means of its rotation and weight. The critical parameters of the proposed method are the rotation speed and the mechanical stress. Using this new method, we thought it would be possible to predict a more realistic disintegration rate in human. To evaluate our hypothesis, the disintegration rates of various placebo RDTs were evaluated using conventional tests (disintegration test, dissolution test), the proposed method, and sensory test in human, and the results were compared.

Experimental

Materials Mannitol was purchased from Towa Chemical Industry Co., Ltd. (Tokyo, Japan). Light Anhydrous Silicic Acid (Aerosil®) was supplied by Nippon Aerosil Co., Ltd. (Tokyo, Japan). Polyvinylpyrrolidone (PVP) and polyvinylalcohol (PVA) were purchased from ISP Technologies (NJ, U.S.A.) and Nihon Synthetic Chemical Co., Ltd. (Tokyo, Japan), respectively. Other chemicals were of special or analytical grades.

Manufacture of RDTs Formulations employed in this study are summarized in Table 1. The test tablets were prepared using two types of binder. RDTs were manufactured by the procedure developed by Morita *et al.*[13] Mannitol was pulverized with a high-speed mixer. Binder was dissolved in a solvent composed of 25% (W/W) ethanol/water. Mannitol and Aerosil were kneaded with the binder solution in order to achieve uniform moisture. Subsequently, the wet powder was compressed by a novel molding tabletting system, which consisted of a molding tabletting machine and a belt dryer (90 °C), developed by Eisai Co., Ltd. (Tokyo, Japan) and Sankyo Seisakusho Co. (Tokyo, Japan). Following drying with the belt dryer, tablets were dried in a tray dryer at 60 °C (DAE-20, Sanwa Kaki Kogyo Co., Ltd., Tokyo, Japan) in order to reduce the loss on drying of the tablets. The diameter of these tablets was 8 mm (flat tablet).

Measurement of Disintegration Time in the Human Sensory Test Twelve healthy volunteers tested the disintegration time of the placebo RDTs (18 samples). Before the test, the mouth cavity was rinsed with a cup of water (200 ml). The tablet was placed on the tongue, and subsequently the

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tongue was gently moved. The time required for the elimination of any residue or fragment of the tablet was measured with a stopwatch.

Conventional Disintegration and Dissolution Test Disintegration time in the conventional disintegration test was measured following the Japanese Pharmacopeia.

Disintegration time in the conventional dissolution test (JP 1st) was measured visually using a stopwatch. The dissolution media was 900 ml-purified water at 37 °C. The rotation speed of the shaft was 50 rpm.

New Disintegration Method Figure 1 shows an illustration of the newly proposed disintegration method. Purified water was used as medium. The medium temperature was set at 37 °C. The RDT was placed on the wire gauze (D), slightly immersed in the medium, and then compressed by the shaft (E). The compression force was easily adjusted using the weight (A). The rotary shaft crushed the RDT, and the RDT was disintegrated into the medium. The optimum rotation speed and weight, 10 rpm and 15 g, respectively, were set according to a previous study.[14] The endpoint is measured visually using a stopwatch.

Results

Physical Properties of RDTs Table 1 describes the formulations for the RDTs employed. PVA and PVP were used as typical binders. Table 2 shows that the increase in binder or water content improved the friability of the RDT. Friability test was performed following Japanese Pharmacopeia. The criterion for friability is "not more than 1%". All samples satisfied this criterion.

Except for hardness, there was not significant change in the important physical properties between the initial and stored samples. In hardness, some sample was slightly decreased.

Disintegration Time in Human Sensory Test As shown in Fig. 2, the disintegration time in the human sensory test was influenced by formulation. The compression force during the tabletting process did not affect the disintegration time. In the initial samples, the disintegration times of RDTs containing PVA (column A—C) were longer than those with PVP in stored samples, the disintegration times of all RDTs using PVA were remarkably delayed.

Disintegration Time Using Conventional Disintegration Test and Dissolution Test When measured with the conventional disintegration test, the disintegration time varied depending on the composition and storage (Fig. 3). The compression force during the tabletting process did not affect the disintegration time. In the initial samples, the disintegration times of RDTs containing PVA were longer than those with PVP. In stored samples, the disintegration times of all RDTs containing PVA were remarkably delayed.

In the conventional dissolution test, disintegration time was not affected by any of the parameters discussed in this study (formulation, storage condition, and compression force in the tabletting process). As shown in Fig. 4, all disintegration times were approximately ten minutes.

Figure 5 shows the relationship between human sensory test and conventional tests. There was no relationship between the disintegration times determined by the disintegration test and those of the dissolution test. Furthermore, no correlation was found between the disintegration times obtained in the dissolution test and the test in human sensory test. However, we observed a significant relationship ($r^2=0.861$) between the disintegration test and the human sensory test. Nevertheless, the slope was far from 1 (0.241).

Disintegration Time Using Newly Proposed Method Figure 6 shows the disintegration times obtained using the newly proposed method for the RDT. Similar to the conventional disintegration test and the human sensory test, the disintegration time was affected by the composition of the

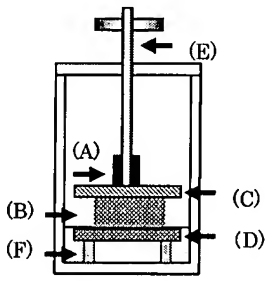

Fig. 1. Apparatus of Proposed New Disintegration Method for RDT

(A) Weight, (B) RDT, (C) wetting sponge, (D) wire gauze, (E) rotary shaft, (F) medium.

Table 1. Formulation of RDTs

	A	B	C	D	E
Mannitol	162.5	162.5	162.2	162.5	162.5
Aerosil®	1	1	1	1	1
PVA	1.5	1.5	1.8		
PVP				1.5	1.5
Water[a)]	(12)	(15)	(18)	(12)	(15)
Ethanol[a)]	(4)	(5)	(6)	(4)	(5)
Total	165	165	165	165	165

a) Removed during drying process.

Table 2. Physical Properties of RDTs (Initial, 60 °C/75%RH 1 Week)

Condition	Initial					60 °C/75%RH 1 week				
Sample	A	B	C	D	E	A	B	C	D	E
Compression (kg)	15	15	15	15	15	15	15	15	15	15
Weight (mg)	170.0	170.5	173.4	168.9	169.9	170.3	170.3	173.1	169.1	170.1
(n=50)	(2.2)	(2.0)	(1.6)	(2.1)	(2.4)	(2.2)	(2.0)	(1.8)	(2.2)	(2.2)
Thickness (mm)	3.61	3.76	3.60	3.61	3.56	3.67	3.78	3.75	3.63	3.54
(n=5)	(0.04)	(0.10)	(0.05)	(0.08)	(0.05)	(0.12)	(0.11)	(0.17)	(0.12)	(0.06)
Hardness (kg)	5.58	4.94	5.03	4.19	3.79	4.85	3.32[a)]	4.44	3.14[b)]	3.26
(n=5)	(0.55)	(0.36)	(0.40)	(0.50)	(0.59)	(0.86)	(0.55)	(0.87)	(0.42)	(0.34)
Friability (%)	0.70	0.60	0.46	0.29	0.17	0.68	0.56	0.41	0.20	0.11
(n=1)										
Loss on drying (%)	0.17	0.20	0.18	0.27	0.29	0.18	0.17	0.22	0.30	0.32
(n=1)										

Mean (S.D.) *a*) $p<0.001$, *b*) $p<0.01$ *vs.* Initial. Other parameter is not significant difference (N.D.).

RDTs.

As shown in Fig. 7, a significant correlation was observed (r^2=0.859) between the newly proposed disintegration method and the human sensory test, and the slope was close to 1 (0.858).

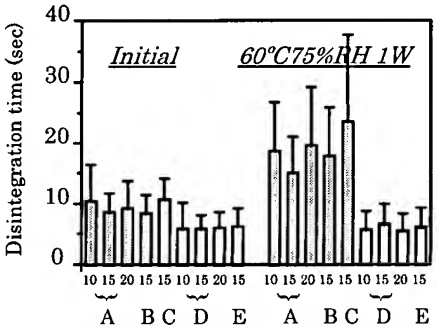

Fig. 2. Disintegration Time of RDTs in Human Sensory Test

Mean (S.D.) value (n=12). 10, 15, 20 were compression force (kg). A—E were sample name.

Discussion

The purpose of this study was to develop a suitable and simple disintegration method for RDTs. Placebo RDTs were prepared with various disintegration characteristics in order to assess our method. In this study, the binder content in the tablets was slightly higher than the optimum and the stress conditions (60 °C/75%RH, 1 week) were too rigorous compared with the conventional accelerated conditions (40 °C/75%RH, 6 months).

Among the physical properties (weight, thickness, hardness, friability, loss on drying, and disintegration time) evaluated for the RDTs, the disintegration time was extremely changed after storage under severe stress conditions (60 °C/75%RH, 1 week).

In the human sensory test, there was a clear difference in

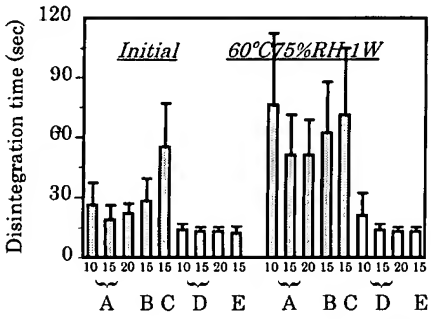

Fig. 3. Disintegration Time of RDTs in Disintegration Apparatus

Mean (S.D.) value (n=6). 10, 15, 20 were compression force (kg). A—E were sample name.

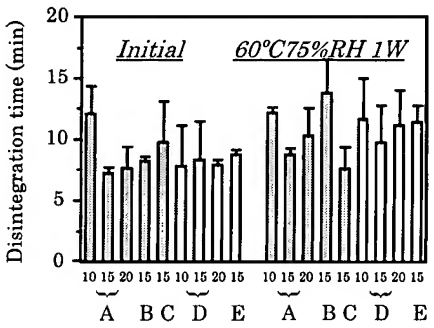

Fig. 4. Disintegration Time of RDTs in Dissolution Apparatus

Mean (S.D.) value (n=3). 10, 15, 20 were compression force (kg). A—E were sample name.

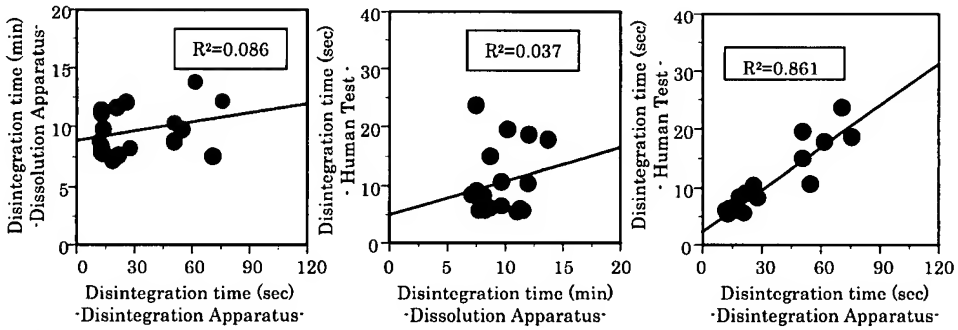

Fig. 5. Relationship between Disintegration or Dissolution Time in Various Test

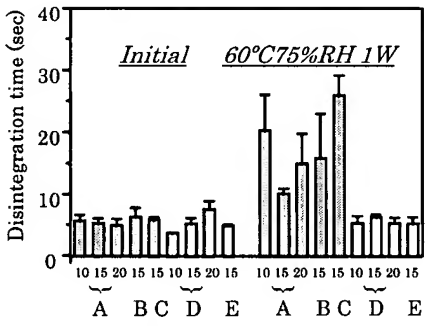

Fig. 6. Disintegration Time of RDTs in New Method

Mean (S.D.) value (n=3). 10, 15, 20 were compression force (kg). A—E were sample name.

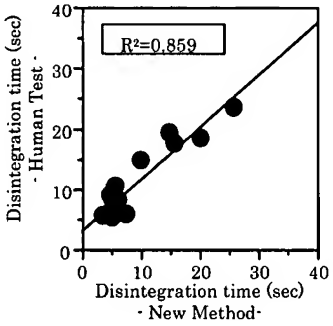

Fig. 7. Relationship between Disintegration Time in New Method and Human Sensory Test

the disintegration times of RDTs containing PVA and PVP in the initial samples. After the storage at 60 °C/75%RH for 1 week, the disintegration rate of RDTs containing PVA was remarkably delayed. In contrast, RDTs including PVP showed no change in the disintegration time after storage.

This effect was observed not only in human sensory test but also in the conventional disintegration test. The effect, however, seemed to be smaller in human sensory test, which could be related to the mechanical stress produced in the mouth. The slope between the disintegration time in the conventional disintegration test and the human sensory test was nevertheless far from 1 (0.241).

There have been several reports on new disintegration methods.[11,13] Bi *et al.* proposed a method using a modified dissolution test apparatus. In this method, the RDT is placed in the sinker, and the sinker is dropped within medium (900 ml 37 °C). Morita *et al.* used a CCD camera to monitor the disintegration time. Both methods are remarkable, but they evaluate the RDT without taking into account the effect of mechanical stress.

Morita *et al.* reported the relationship between oral disintegration time (*in vivo*) and disintegration time (*in vitro*) calculated using the new method for each binder. However, the correlation was far from 1, and the method differed with respect to each type of binder.[13]

Our method, in contrast, is widely applicable to RDTs without the need to consider the type of binder used in the formulation. Moreover, good correlation was obtained between the disintegration time determined *in vitro* and *in vivo* for all RDT samples even stored samples; the slope was near to 1 (0.858). The results demonstrate that the mechanical stress induced by the rotary shaft (rotation and weight) is one of the most important and critical factors for disintegration of the RDT. Another critical factor might be the amount of water used in the test method. In the above methods, a large amount of water is utilized, so RDT was immersed in the 900 ml water. However, this condition does not resemble the actual conditions in the oral cavity. In fact, the saliva volume was very small, and these small amounts of saliva penetrate into the RDTs. The method we propose utilizes only a limited amount of water to allow the penetration of water. From this point of view, our proposed method also presents a clear advantage.

In conclusion, we were able to establish a suitable and simple disintegration method for RDTs, which has good correlation with disintegration in the human mouth. It presents clear advantages with respect to current available methods and thus, might provide a novel approach for the determination of the disintegration time of the RDT.

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